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A role for caspase-8 and TRAIL-R2/DR5 in ER-stress induced apoptosis

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Running title: DR5 and caspase-8 in ER-stress induced apoptosis

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Text

Glab and colleagues[1] examine in a recent paper apoptosis induced by some driverss of endoplasmic reticulum (ER) stress. They conclude that in contrast to a previously published report[2] , DR5/TRAIL-R2 and caspase-8 are universally dispensable in ER stress-induced apoptosis. We argue here that their own data and other published reports indicate that in many models, DR5 and/or caspase-8 are essential players in apoptosis mediated by the unfolded protein response (UPR), upon chronic ER stress.

The authors analyze the effects of knocking down caspase-8, DR5, Bim and Bid. The authors describe that Bim is not essential at least in one of their three models. In line with these results, we and other authors have shown that Bim is dispensable for apoptosis mediated by the UPR in some systems even though the protein is induced; in these cases the apoptotic cell death can be attributed to Noxa or to Caspase-8 (please see table 1 in Ref. 3, and Refs. 4-6). We find inconsistent that the title and abstract mention that caspase-8 and DR5 are dispensable in ER stress-induced apoptosis but not that Bim is not required in their system, in contrast to earlier findings (Ref. 7).

The authors' own data (Ref. 1, Fig. 3c) indicates that Bid is crucial in one of their models: HCT116. Moreover, although the authors report a drastic reduction of apoptosis with some treatments, they also show that over 20% of Bax, Bak deficient cells undergo apoptosis (Ref.1, Fig. 2E,F). We suggest that this apoptosis is mediated by caspase-8 as described in Bax, Bak deficient HCT116 and MEFs treated with UPR-inducing stimuli[4,6]. Indeed, a certain role for caspase-8 is shown by the authors in Supplementary fig. 2 but this is not mentioned in the title or abstract.

Regarding the role of DR5, authors do observe reduction of cell death in one knock-out clone. Importantly, the authors seem focused to disprove one study, while ignoring numerous studies that have shown a role of DR5 and caspase-8 in apoptosis activated by different UPR-inducing stimuli such as thapsigargin or glucose deprivation[3,8,9], table 1). Moreover, it is possible that in cells knocked out for DR5, it is DR4 or other death receptors (reviewed in Ref. 6) that may be participating in caspase-8 activation and Bid cleavage, as we have recently described in ATF4-mediated cell death[6].

Altogether, these data indicate that DR5, caspase-8, Bim, Bid and Noxa are required for ER stress and UPR-mediated death in a cell type-dependent manner.

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Table 1. Examples of reports showing a role for caspase-8 and/or DR5 in apoptosis mediated by components of the UPR or the Integrated Stress Response (ISR)

Mediator	Stimulus	Cell type	Reference
Caspase-8	Tunicamycin	HEK293, MCF7	Tomar *et al* 2013, PMID 24021263
		bax$^{-/-}$*bak*$^{-/-}$ BMK	Ullman *et al* 2011, PMID 21576355
	Bortezomib/MG132	HEK293, MDAMB231, MCF7	Pan *et al* 2001, PMID 21628531
Caspase-8, FADD	Bortezomib/MG132	Atg5+/+ and Atg5-/- MEFs,FADD+/+ and FADD-/- MEFs, KG-1	Young *et al* 2012, PMID 22362782
		HeLa, H460, MEFs	Laussmann *et al* 2011, PMID 21455219
	Tunicamycin, Thapsigargin	CASP9-/- MEFs, bax/Bak-/- MEFs	Deegan *et al* 2014, PMID 25470234
Caspase-8, RIPK1	Tunicamycin	MEFs and HEK293T	Estornes *et al* 2014, PMID 25476903
DR5	Thapsigargin	HCT116, LNCaP, A2780S and DU145	Yamaguchi *et al* 2004, PMID 15322075
DR5, Caspase-8	Thapsigargin, Tunicamycin	MCF10A	Martín-Pérez *et al* 2014, PMID 24453000
	Thapsigargin	HCT116, SK-MES-1, KSM11, RPMI-8226	Lu *et al* 2014, PMID 24994655
	CB-5083	HCT116	Anderson *et al* 2015, PMID 26555175
DR5, DR4	Glucose deprivation	HCT116, HCT116 Bax, Bak (-/-), HeLa	Iurlaro *et al* 2017, PMID 28242652
	Tunicamycin, thapsigargin, brefeldin A	HCT116, MDA-MB-231, H1703	Dufour et al 2017, PMID 28039489
DR4/TRAIL-R1	Tunicamycin, Thapsigargin	A549	Li *et al* 2015, PMID 25770212